

Replacement Claim Section

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application. Please insert the phrase "I claim:" at the beginning of the claims just prior to claim 1.

Listing of Claims:

I claim:

Claim 1 (currently amended). A method for diagnosis of Alzheimer's disease in a human subject which comprises screening for the presence of a cell cycle regulatory defect at the G1/S phase transition in non-neuronal cells of the human subject.

Claim 2 (original). A method according to claim 1 wherein a reduction in the effectiveness of the checkpoint control at the G1/S transition is taken as an indication that the subject has Alzheimer's disease.

Claim 3 (original). A method according to claim 1 or claim 2 wherein screening for the presence of a cell cycle regulatory defect at the G1/S phase transition is carried out by: inducing cell division in the non-neuronal cells and testing the responsiveness of the cells to a cell division inhibitor substance, wherein a reduced responsiveness to the cell division inhibitor substance in cells from the subject, as compared to control cells not having a cell cycle regulatory defect at the G1/S phase transition, is taken as an indication of the presence of a cell cycle regulatory defect at the G1/S phase transition.

Claim 4 (original). A method according to claim 3 wherein the cell division inhibitor substance is a specific G1 inhibitor.

Claim 5 (original). A method according to claim 1 or claim 2 wherein screening for the presence of a cell cycle regulatory defect at the G1/S phase transition is carried out by: inducing cell division in the non-neuronal cells and testing the responsiveness of the cells to a stimulus that induces cell cycle arrest, wherein a reduced responsiveness to said stimulus in-cells from the subject, as compared to control cells not having a cell cycle regulatory defect at the G1/S phase transition, is taken as an indication of the presence of a cell cycle regulatory defect at the G1/S phase transition.

Claim 6 (original). A method according to claim 5 wherein the stimulus that induces cell cycle arrest is selected from oxidative stress, ionising radiation, hypoxia, or UV radiation.

Claim 7 (currently amended). A method according to ~~any one of claims~~ claim 3 ~~to 6~~ wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus that induces cell cycle arrest is tested by a cell proliferation assay, relatively higher proliferative activity in cells from the subject, as compared to control cells not having a cell cycle regulatory defect at the G1/S phase transition, following treatment with the cell division inhibitor or stimulus that induces cell cycle arrest being taken as an indication of the presence of a cell cycle regulatory defect at the G1/S phase transition.

Claim 8 (currently amended). A method according to ~~any one of claims~~ claim 3 ~~to 6~~ wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus that induces cell cycle arrest is tested by calculating the relative lengthening of the G1 phase of the cell cycle in cells from the subject, a reduced relative lengthening of the G1 phase in the presence of the cell division inhibitor substance or stimulus in said cells, as compared to control cells not having a cell cycle regulatory defect at the G1/S phase transition, being taken as an indication of a cell cycle regulatory defect at the G1/S phase transition.

Claim 9 (currently amended). A method according to ~~any one of claims~~ claim 3 ~~to 6~~ wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus that induces cell cycle arrest is tested by analysis of expression of a cell cycle regulatory protein or an mRNA encoding a cell cycle regulatory protein.

Claim 10 (original). A method as claimed in claim 9 wherein the cell cycle regulatory protein is selected from the group consisting of CDKN3, p15ink4B, p16ink4A, p19ink4D, p27kip1, p21cip1, p57kip2 and TP53.

Claim 11 (original). A method according to claim 5 wherein the stimulus that induces cell cycle arrest is DNA damage and the responsiveness of the cells to the cell this stimulus is tested by analysis of expression of a DNA damage-response element.

Claim 12 (original). A method according to claim 11 wherein the DNA damage-response element is selected from the group consisting of TP53, Gadd34, Gadd45A, Gadd45B, Gadd45G, Gadd153 and PCNA.

Claim 13 (currently amended). A method according to ~~any one of claims~~ claim 3 ~~to 6~~ wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus that induces cell cycle arrest is tested by assessment of cell viability or cell death, wherein increased cell survival or a reduced degree of cell death in said cells, as compared to control cells not having a cell cycle regulatory defect at the G1/S phase transition, following exposure to the cell division inhibitor or other stimulus that induces cell cycle arrest is taken as an indication of the presence of a cell cycle regulatory defect at the G1/S phase transition.

Claim 14 (currently amended). A method according to ~~any one of claims~~ claim 3 ~~to 6~~ wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus which elicits cell cycle arrest is tested by analysis of expression of a cell death related protein or an mRNA encoding a cell death related protein.

Claim 15 (original). A method according to claim 14 wherein the cell death related protein is a member of the bcl-2 family of proteins.

Claim 16 (currently amended). A method according to ~~any one of claims~~ claim 3 ~~to 6~~ wherein the responsiveness of the cells to the cell division inhibitor substance or stimulus which elicits cell cycle arrest is tested by assessment of DNA content of the cells with or without cell cycle analysis.

Claim 17 (currently amended). A method according to ~~any one of claims~~ claim 1 ~~to 16~~ wherein the non-neuronal cells are lymphocytes.

Claim 18 (currently amended). A method according to ~~any one of claims~~ claim 1 ~~to 17~~ for diagnosis of sporadic Alzheimer's disease.

Claim 19 (withdrawn). A method for use in diagnosis of Alzheimer's disease in a human subject which comprises screening for the presence in the genome of said subject of at least one mutation or allelic variant in a cell cycle regulatory gene, wherein the presence of a

mutation or allelic variant in a cell cycle regulatory gene is taken as an indication of Alzheimer's disease.

Claim 20 (withdrawn). A method of determining any genetic basis for Alzheimer's disease in a human subject, which comprises screening the genome of said subject for the presence of mutations or allelic variants in a cell cycle regulatory gene.

Claim 21 (withdrawn). A method of screening a human subject for pre-disposition to Alzheimer's disease which comprises screening for the presence in the genome of said subject of at least one mutation or allelic variant in a cell cycle regulatory gene.

Claim 22 (withdrawn). A method according to any one of claims 19 to 21 which comprises screening for the presence of mutations or allelic variants in at least one gene selected from: CDKN3, p15ink4B, p16ink4A, p19ink4D, p27kip1, p21cip1, p57kip2 and TP53.

Claim 23 (withdrawn). A method according to claim 22 which comprises genotyping for one or more of the p21E2 A/B polymorphism, the p57E2A A/B polymorphism, or the p57E2B A/B polymorphism.

Claim 24 (withdrawn). A method for use in diagnosis of Alzheimer's disease in a human subject which comprises screening for the presence in the genome of said subject of at least one mutation or allelic variant in a gene encoding a DNA repair enzyme, wherein the presence of a mutation or allelic variant in such a gene is taken as an indication of Alzheimer's disease.

Claim 25 (withdrawn). A method of determining any genetic basis for Alzheimer's disease in a human subject, which comprises screening the genome of said subject for the presence of mutations or allelic variants in a gene encoding a DNA repair enzyme.

Claim 26 (withdrawn). A method of screening a human subject for pre-disposition to Alzheimer's disease which comprises screening for the presence in the genome of said subject of at least one mutation or allelic variant in a gene encoding a DNA repair enzyme.

Claim 27 (withdrawn). A method according to any one of claims 24 to 26 which comprises screening for the presence of mutations or allelic variants in at least one gene selected from: Ku70, Ku80, Ku86, NDHII, BLM, RECQL, RECQL4 and RECQL5.

Claim 28 (withdrawn). A method of identifying compounds having potential pharmacological activity in the treatment of Alzheimer's disease, which method comprises steps of: analysing the regulation of the G1/S transition in non-neuronal cells, which cells exhibit a cell cycle regulatory defect at the G1/S phase transition, in the presence and absence of a test compound, wherein a test compound which results in correction of the regulatory defect at the G1/S transition in said cells is identified as having potential pharmacological activity in the treatment of Alzheimer's disease.

Claim 29 (withdrawn). A method of determining whether a pharmacological agent is likely to be of benefit in the treatment of Alzheimer's disease in a particular human individual, which method comprises: analysing the regulation of the G1/S transition in cells from said individual, which cells are non-neuronal cells that exhibit a cell cycle regulatory defect at the G1/S phase transition, in the presence and absence of the pharmacological agent, wherein a pharmacological agent which results in correction of the regulatory defect at the G1/S transition in said cells is identified as likely to be of benefit in the treatment of Alzheimer's disease in said individual.